DT-2179

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPLICANT(S)	:	Wolfgang Barnikol
SERIAL NO.	:	08/869,406
FILED	:	June 5, 1997
FOR	:	Method for the Preparation of Molecularly Uniform Hyperpolymeric Hemoglobin
EXAMINER	:	Anish Gupta GROUP ART UNIT: 1654

Mail Stop **Appeal Brief - Patents**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

Sir:

This is a Brief in support of an appeal from the Final Rejection of claims 6-9 and 11-15 by the Examiner.

The Commissioner is hereby authorized to charge the fee required under 37 C.F.R. §1.17(c) in the amount of $160.00 and any additional fee which may be required, or credit an overpayment to our Deposit Account No. 50-0955. A duplicate of this sheet is enclosed.

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I. REAL PARTY IN INTEREST

The real party in interest is the inventor, Wolfgang Barnikol.

II. RELATED APPEALS AND INTERFERENCES

None

III. STATUS OF CLAIMS

The subject application has been filed with sixteen (16) claims. During the prosecution, claims 1-5, 10 and 16 were canceled. Claims 6-9 and 11-15 are now pending in the application for appeal purposes.

The status of the claims is as follows:

Claims allowed: None

Claims objected to: None

Claims rejected: Claims 6-9 and 11-15.

IV. STATUS OF AMENDMENTS

All amendments were entered by the examiner prior to the Final Rejection.

V. SUMMARY OF INVENTION

The present invention relates to a method for the preparation of molecularly uniform hyperpolymeric hemoglobim from a solution containing

only cross-linked hyperpolymeric hemoglobin molecules with a size up to (5-10)x 100 times of a size of quaternary hemoglobin molecular (page 7, lines 2-4 from the bottom). The method includes performing fractional precipitation of the solution in $(NH4)_2$ SO_4 as a precipitation agent (page 13, fourth line from the bottom) for at least 30 minutes (page 15, line 5), fractionating chromatographically in the solution and fractionation dissolution of the solution (page 14, lines 11-23), and performing at least one of the steps above or any combination of the steps above, and separating the hyperpolymeric hemoglobin into different fractions based on its molecular weight (page 9, line 20 to page 10, line 2).

According to another embodiment of the inventive method, a preparative chromatographical fractionation is performed by using gel-permeating chromatography (page 11, lines 3-6), and fractionation by a partial dissolution of precipitate of hemoglobin hyperpolymers is performed (page 14, lines 11-23). Alternatively, only one of the above-mentioned steps is performed, with separating the hyperpolymeric hemoglobin into different fractions based on its molecular weight (page 9, line 20 to page 10, line 2).

VI. ISSUES

The claims presently pending in the subjection application, namely, claims 6 and claims 11, and claims 7-9 dependent on claim 6, and claims 12-15 dependent from claim 11, stand rejected under 35 U.S.C. §103(a) as being unpatentable over Potzschke et al., claims 6 and 11, and claims 7-9 dependent from claim 6, and 12-15 dependant from claim 11, stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Potzschke et al. in view of Banhard. The issues under consideration is (i) whether the reference set forth in the Final Office Action anticipates claims 6-9 and 11-15, (ii) whether it would have been obvious to combine the references in a manner set forth in the Final Office Action, (iii) in the affirmative, whether the combination set forth in the Final Office Action indeed makes claims 6-9 and 11-15 unpatentable.

VII. GROUPING OF CLAIMS

Claim 6 and 11 are independent claims pending in the subject application. The novel features of the present invention are defined in claims ;6 and 11, and it is respectfully submitted that claims 6 and 11 is patentably distinct over the prior art.

Claims 6-9 depend from claim 6 and stand or fall together with claim 6.

Claims 12-15 depend from claims 11 and stand or fall together with claim 11.

VIII. ARGUMENT

Claims 6-14 and 16 were rejected as being read on by the cited prior art Poetzschke and Barnikol, Biomater. Art Cells and Immob. Biotechn., 20, 287-91 (1992). Applicant has argued that the method described in Poetzschke described only an analytical method and not a preparative method as is being claimed. The rejection was based on the assertion that the claims did not limit themselves to a preparative method, but also described an analytical method. The claims have been amended to more clearly reflect that the claimed method is a preparative one. Poetzschke does not anticipate a preparative method. The analytical and preparative use of a physiochemical method are not the same. That a method functions on one scale says nothing about the possibility of the ability to scale-up the method. An analytical method merely goes to the ability to detect the distribution of hydrodynamic molecular weights in a sample, but in no way predicts the ability to separate

usable samples. In an analytical method, the test sample is small and is lost by the method of detection. In a preparative method, the sample must survive the detection process (preferably with a high yield). Thus, that one is able to detect the separation of cross-linked hyperpolymeric hemoglobin by its molecular weight, is no guarantee that one can preserve such fractions separated by molecular weight.

Claims 6-16 were rejected as being unpatentable over Poetzschke in view of U.S. Patent 4,136,093 (Bonhard). The Poetzschke reference has been overcome by the amendments to the claims as discussed above. Additionally, claims 6-16 were rejected on the combination of Poetzschke and Bonhard because "one would expect the non-cross-linked hemoglobin to separate out from the cross-linked hemoglobin as taught in Bonhard" when ammonium sulfate is applied to the sample. While that may be true, the method claimed uses ammonium sulfate to separate cross-linked hemoglobin from cross-linked hemoglobin to obtain a cross-linked hemoglobin with a smaller molecular weight distribution. Such a procedure is not taught by Bonhard.

Appellants respectfully submit that a prima facie case of obviousness has not been made. Under MPEP § 2143, a prima facie case of obviousness requires that three basic criteria be met.

> First, there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Appellant respectfully submit that the foregoing criteria have not been met.

There is no suggestion, incentive or motivation in either Potzche or Bonhard for the combination on which the claims were rejected. A statement that it would have been obvious to one skilled in the art to make modifications to the references is not sufficient to establish a *prima facie* case of obviousness. MPEP § 2143.01 relying on *Ex Parte Levengood*, 28 U.S.P.Q.2d 1300 (Bd. Pat. App. & Inter. 1993). In order to establish a *prima facie* case of obviousness, "it

is necessary for the Examiner to present *evidence*, preferably in the form of some teaching, suggestion incentive or inference in the prior art, or in the form of generally available knowledge, that one having ordinary skill in the art *would have been led* to combine the relevant teachings." *Id.* at 1301 (emphasis in original).

The Federal Circuit has held that a claimed invention was not obvious, where "[c]onspicuously missing from [the] record is any *evidence*, other than the PTO's speculation (if it be called evidence) that one skilled in the art would have been motivated to make the modification of the prior art "necessary to arrive at the claimed invention." *In re* Jones, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992).

The Court of Appeals for Federal Circuit clearly stated:

> The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior suggested the desirability of the modification,
>
> and further
>
> It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teaching of the prior art so that the claimed invention is rendered obvious.

In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992).

In the *In re Fritch* holding only confirmed a long established view that obviousness should not be read "into an invention on the basis of Applicant's own statements", that the prior art must be viewed "without reading into that art Appellant's teachings", and that the teachings of the prior art should, "*in and of themselves and without the benefits of Appellant's disclosure* (emphasis in the original text), make the invention as a whole, obvious." *In re Sponnoble*, 160 U.S.P.Q. 237, 243 (CPA 1969).

There is no suggestion in the applied references for a combination set forth in the Office Action.

Appellant respectfully submits that a *prima facia* case of obviousness has not been made.

CONCLUSION

In view of the above, it is respectfully submitted that the rejection of claims 6-9 and 11-15 under 35U.S.C. §102(b) as being anticipated by Potzschke et al and under 35 U.S.C. §103(a) as being unpatentable over Potzschke in view of Bonhard is improper and should be reversed.

Respectfully Submitted,

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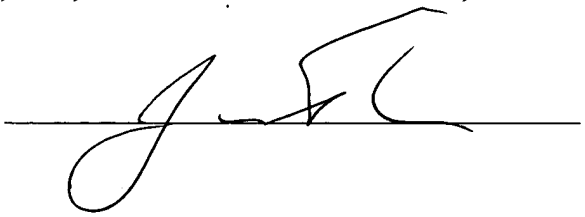
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail and address to: Commissioner for Patent, P.O. Box 1450, Alexandria, VA, VA 22313 on October 7, 2003.



APPENDIX "A"

Claims on Appeal:

6. A method for preparation of molecularly uniform hyperpolymeric hemoglobins from a solution containing only cross-linked hyperpolymeric hemoglobin molecules with a size which is up to (5-10) x 100 times a size of quaternary hemoglobin molecules comprising the steps of:

Performing fractional precipitation of the solution in $(NH4)_2\ SO_4$ as a precipitation reagent for at least 30 minutes,

Fractionating chromatographically in the solution,

Performing a partial fractionation dissolution of the solution, or

Performing at least one of the steps above or any combination of the steps above; and

Separating the hyperpolymeric hemoglobin into different fractions based on its molecular weight.

7. The method according to claim 6, comprising adding a bifunctional crosslinking agent for the crosslinking process.

8. The method according to claim 7, wherein the crosslinking agent is carried out by utilizing glutaraldehyde or 2,5-diisocyanate benzene sulfonate.

9. The method according to claim 6, wherein chromatographic fractionation is performed with Sephacryl S-400HR and the solvent utilized has the following composition:

NaCL 144 mmol/1;

HEPES Buffer 10 mmol/l; and

NaN3 200 mg/1.

11. A method for the preparation of molecularly uniform hyperpolymeric hemoglobins with uniform molar masses from solutions containing cross-linked hyperpolymeric hemoglobin molecules with a size which is up to (5-10) x 100 times a size of (quaternary structured) native hemoglobin molecules, comprising the steps of:

performing fractional precipitation of the solution by adding a precipitation reagent;

performing a preparative chromatographical fractionation by using gel-permeation chromatography,

performing fractionation by partial dissolution of a precipitate of hemoglobin hypopolymers; or

performing at least one of the steps above or any combination of the steps above; and

separating the hyperpolymeric hemoglobin into different fractions based on its molecular weight.

12. The method according to claim 11, comprising hemoglobin hyperpolymers synthesized by using bifunctional crosslinking agents.

13. The method according to claim 11, where the crosslinkers used are glutaraldehyde or 2,5-diisothiocyanatobenzene sulfonate.

14. The method according to claim 11, wherein the fractional precipitation is performed by adding ammonium sulphate ($(NH_4)_2SO_4$) to a concentrated hemoglobin hyperpolymers solution and a reaction time of at least 30 Minutes.

15. The method according to claim 11, wherein the chromatographic fractionation is performed with Sephacryl S-400 HR gel and the solvent used has the composition:

NaCL	144 mmol/l;
HEPES Buffer	10 mmol/l; and
NaN_3	100 mg/l.

APPENDIX "B"

1. Ex Parte Levengood, 28 U.S.P.Q. 1300 (Bd. Pat. App. & Inter. 1993);

2. In re Johnes, 21 U.S.P.Q.2d, 1941 (Fed. Cir. 1992);

3. In re Fritch, 23 U.S.P.Q.2d, 1780, 1783 (Fed. Cir. 1992);

4. In re Sponnoble, 160 U.S.P.Q. 237, 243 (CCPA 1969).